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Therapy of Refractory Symptomatic Atrial Fibrillation and Atrial Flutter: A Staged Care Approach With New Antiarrhythmic Drugs

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One hundred nine patients with recurrent episodes of symptomatic atrial fibrillation or flutter, or both, who had failed one to five previous antiarrhythmic drug trials were treated with propafenone and, subsequently, sotalol if atrial fibrillation recurred. The clinical profile of the study group was as follows: age 63 ± 13 years, left atrial anteroposterior dimension 4.4 ± 0.9 cm and left ventricular ejection fraction 57 ± 14%. Paroxysmal atrial fibrillation occurred in 56 patients (51%) and chronic atrial fibrillation occurred in 53 patients (49%).

After loading and dose titration phases were completed, the maintenance doses of drugs were 450 to 900 mg/day for propafenone and 160 to 960 mg/day for sotalol. Life table estimates of the duration of freedom from atrial fibrillation were constructed for each drug trial. The percent of patients free of recurrent symptomatic arrhythmia at 6 months was 39% for propafenone and 50% for sotalol. The cumulative proportion of patients successfully treated with propafenone or sotalol, or both, by 6 months was 55% and remained relatively constant beyond that point. The incidence of intolerable side effects necessitating discontinuation of therapy ranged from 7% to 8%

Thus, despite previous unsuccessful drug trials, a substantial proportion of patients with recurrent symptomatic atrial fibrillation refractory to conventional therapy can be treated successfully and safely with newer antiarrhythmic drugs. Treatment failures tend to occur early in the course of follow-up, permitting easy identification of candidates for alternative therapeutic approaches.

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Atrial fibrillation, an extremely common cardiac arrhythmia, is estimated to affect 2% to 4% of adults >60 years of age (1,2). Conventional antiarrhythmic drugs (quinidine, procainamide and disopyramide) are widely prescribed to prevent recurrence of atrial fibrillation, even though the relative benefits of treatment with such agents have never been substantiated in large scale randomized clinical trials. Because these agents often fail to prevent recurrence of atrial fibrillation or frequently must be discontinued because of intolerable drug-related side effects, attention has focused on the use of alternative agents in the management of patients with atrial fibrillation or flutter. Among the newer antiarrhythmic agents, compounds that markedly slow conduction in the atrial myocardium (class IC drugs) and prolong the effective refractory period of atrial myocardial cells (class III drugs) have electrophysiologic profiles suggesting that they would be potent antifibrillatory agents. Previously published studies with agents such as propafenone (3–7) and sotalol (8–10) have reported favorable clinical results. However, limited data are available on the long-term effectiveness of such drugs. Detailed clinical investigations have not been carried out to evaluate these new antiarrhythmic agents alone or in combination for patients with recurrent symptomatic atrial fibrillation.

The objective of this study was to examine the efficacy and safety of sequential antiarrhythmic drug trials with propafenone and sotalol for the long-term suppression of recurrent symptomatic atrial fibrillation or flutter, or both, that was inadequately treated by conventional type IA antiarrhythmic drugs. The protocol was designed to simulate clinical practice and consisted of a series of two drug trials using the technique of upward titration of antiarrhythmic dosage after recurrence of atrial fibrillation. A previous report (3) from our group described observations made

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between March 1985 and June 1987 and included a sample size of only 60 patients; the data analysis was restricted exclusively to treatment with propafenone. The present report provides data on nearly twice the number of patients with approximately 2 additional years of follow-up and includes the results of treatment with sotalol in addition to propafenone.

Methods

Study patients. *Entry criteria.* Between March 1985 and March 1989 patients referred from the medical services of the Brigham and Women's Hospital, Beth Israel Hospital and Children's Hospital Medical Center were evaluated for inclusion in the protocol. Entry criteria included: 1) age >18 years; 2) electrocardiographic (ECG) documentation of a history of atrial fibrillation, atrial flutter or an ECG hybrid of the two rhythms (atrial flutter/fibrillation); 3) a past history of at least one unsuccessful previous trial of suppressive antiarrhythmic therapy with one or more of the following conventional drugs: quinidine, procainamide or disopyramide (past therapy with these conventional agents was considered unsuccessful if atrial fibrillation [or atrial flutter, or both] recurred despite therapeutic doses or intolerable drug-related side effects occurred necessitating discontinuation of the drug regardless of the adequacy of arrhythmia suppression); and 4) clinical evidence that the development of atrial fibrillation or flutter was reproducibly associated with symptoms recognized by the patient, such as lightheadedness, palpitation, dyspnea or syncope.

Exclusion criteria. Patients were excluded from the study if one or more of the following conditions were present: 1) acute myocardial infarction within 1 week of entry into the trial; 2) cardiogenic shock; 3) atrial fibrillation or flutter, or both, that was transient resulting from an unresolved acute or subacute illness such as pneumonia, pulmonary embolism, recent cardiac surgery or uncontrolled congestive heart failure (patients with pericarditis were considered for inclusion in the trial only if they had a chronic relapsing form of the disease); 4) acutely deteriorating hepatic or renal function; and 5) therapy with amiodarone within 12 months, provided maintenance therapy with amiodarone had been prescribed for ≥1 month. Patients with left ventricular ejection fraction <20% or a history of severe bronchospastic lung disease were excluded from treatment with sotalol (see below).

Protocol design. The protocol consisted of open label drug trials with propafenone (stage 1) and sotalol (stage 2). All patients were initially treated with propafenone and only underwent a trial with sotalol after documented recurrence of atrial fibrillation or flutter on a maximally tolerated dose of propafenone or when intolerable side effects developed necessitating discontinuation of the drug. Each drug trial consisted of three phases that were related to drug dosing: a loading phase, a dose titration phase and a long-term maintenance phase (Table 1). The order of the drug trials was designed to minimize exclusion because of poor left ventricular function or bronchospasm by selecting propafenone as the first drug.

Table 1. Dosage Schedule

Stage	Drug	Loading Dose (mg)	Dose Titration Range (mg/day)	Maintenance Dose Range (mg/day)
1	Propafenone	150–300	450–900	450–900
2	Sotalol	80–160	160–960	160–960

For both the propafenone and sotalol trials, all patients were hospitalized in an ECG telemetry ward during the loading phase and initial dose titration phase. Before patient entry into the protocol, all antiarrhythmic drugs were discontinued. When clinically feasible, agents being used to control the ventricular rate (for example, digitalis glycosides, beta-adrenergic blocking agents, verapamil and diltiazem) were also discontinued to eliminate any confounding electrophysiologic effects that could interfere with interpretation of the impact of the study drugs.

Before enrollment, all patients were classified as having paroxysmal atrial fibrillation or flutter or chronic atrial fibrillation or flutter on the basis of the predominant pattern exhibited by their arrhythmia in the preceding month. Individuals whose arrhythmia was characterized by recurrent self-terminating episodes, usually no more than 24 to 48 h in duration and interspersed with long periods of sinus rhythm, were designated as having paroxysmal atrial fibrillation. Patients in whom atrial fibrillation or flutter was the predominant and chronic rhythm, and in whom sinus rhythm had only been observed transiently after previous attempts at electrical or pharmacologic cardioversion, were designated as having chronic atrial fibrillation.

Recent data (11–14) suggest that atrial fibrillation and atrial flutter may have a common electrophysiologic mechanism, namely, reentry within the atrial myocardium. Electrocardiographic patterns in individual patients frequently alternate spontaneously between atrial fibrillation and atrial flutter or may appear as a hybrid of the two rhythms because they may coexist in different regions of the atria at the same time. No attempt was made during this trial to differentiate atrial fibrillation from atrial flutter. In this report, the term atrial fibrillation will signify both types of ECG patterns.

Drug treatment schedule (Table 1). At the inception of each drug trial, written informed consent was obtained before the loading phase was initiated. All consent forms were approved by the Committee for the Protection of Human Subjects from Research Risks at the Brigham and Women's Hospital. During the titration phase with propafenone or sotalol, at least 48 to 72 h was allowed to elapse

between dose changes to permit steady state to be achieved. Upward dose titration with propafenone or sotalol took place over several days to weeks, depending on the clinical response. For patients with chronic atrial fibrillation, propafenone was increased to a maximum of 900 mg/day, and direct current cardioversion was performed in those individuals in whom sinus rhythm had not been restored pharmacologically. In the case of sotalol, direct current cardioversion was performed in patients with chronic atrial fibrillation when the daily dose had been titrated to ≥320 mg. For patients with chronic atrial fibrillation taking sotalol who subsequently had recurrent atrial fibrillation after an initial successful cardioversion, one or more additional cardioversion procedures were performed as needed with higher doses. In patients with paroxysmal atrial fibrillation treated with propafenone or sotalol, each time the arrhythmia recurred the dose of the study drug was increased as tolerated to a maximum of 900 mg/day for propafenone and 960 mg/day for sotalol. Thus, several recurrences of atrial fibrillation (while the patient was receiving incremental dosages of the drug) were permitted before a trial was considered unsuccessful.

During each stage of the drug trial, the only indication for a downward adjustment in drug dose during the long-term maintenance phase was the appearance of drug-related side effects or the development of a rate-corrected QT interval ≥0.5 s on the ECG, or both. Serum concentrations of the study drugs were not routinely measured and were not used to modify dosage schedules. The dose reported for each patient represents the highest tolerated dose of either propafenone or sotalol during the long-term maintenance phase.

Documentation of recurrence of arrhythmia and drug-related side effects. All patients and referring physicians were instructed to confirm any suspected recurrence of atrial fibrillation during the maintenance phase of each stage. This was accomplished by recording a 12 lead ECG, 24 h ambulatory ECG or rhythm strip obtained by telemetry or telephone ECG transmitter. To maximize the probability of documenting atrial fibrillation recurrence and to determine the number of months between the beginning of the maintenance phase and the recurrence of atrial fibrillation, all patients were given a telephone ECG transmitter at the time of hospital discharge. To ensure that patients would have a transmitter available when they were at maximal risk (that is, the first few months after restoration of sinus rhythm), telephone transmitters were reassigned as needed from subjects who had been free of arrhythmia the longest (>3 to 6 months).

All patients were evaluated by one of the study physicians or a specially trained cardiovascular research nurse, or both, every 3 months for determination of cardiac rhythm and review of possible drug-related side effects. Whenever patients reported symptoms suggestive of recurrence of atrial fibrillation, more frequent visits were arranged. The telephone ECG transmitter system was utilized not only for documentation of atrial fibrillation recurrence, but also to maintain contact between the patient and study personnel and to ensure compliance with the protocol.

Data collection, longitudinal follow-up evaluation and study termination. Before enrollment into the protocol, baseline demographic data were recorded, including all relevant cardiac diagnoses, echocardiographic examination for evaluation of underlying cardiac disease, measurement of left atrial size and determination of left ventricular ejection fraction, and the number of months elapsed since the original ECG-documented diagnosis of atrial fibrillation as determined from medical records. Among patients with chronic atrial fibrillation, the number of these undergoing pharmacologic conversion to sinus rhythm was noted for each stage. When direct current cardioversion was required to restore sinus rhythm, an energy titration technique was utilized to establish the minimal amount of energy needed to terminate atrial fibrillation.

All patients were followed up for the duration of the time they were receiving study medication. The primary end point of the trial was the duration of sinus rhythm at each stage as measured from the date of the most recent cardioversion procedure in the chronic atrial fibrillation group and the date 48 h after initiation of the final maintenance dose in the paroxysmal atrial fibrillation group. At the time of the first ECG-documented symptomatic recurrence of atrial fibrillation or whenever intolerable drug-related side effects occurred that necessitated withdrawal of the drug, the current stage was considered to be unsuccessful and patients were advanced to the next stage of the protocol.

Statistical analysis. Data analysis was performed on observations made through March 1989. Patient response to treatment during each drug trial was classified into one of the following three categories: *success* (absence of recurrent atrial fibrillation or intolerable side effects for the duration of follow-up), *relapse* (any recurrence of atrial fibrillation during follow-up once sinus rhythm was established and the patient was in steady state on drug treatment) and *failure* (recurrence of atrial fibrillation or intolerable side effects or both, during follow-up). For each patient entering the various stages of the protocol, the time to first recurrence of atrial fibrillation or development of intolerable side effects was noted. These primary end point data were analyzed using the product limit method of Kaplan and Meier to construct actuarial estimates of the proportion of patients free of any symptomatic recurrences of atrial fibrillation over time for each of the therapeutic stages (15,16). Patients who remained in sinus rhythm were excluded from the study when and if they were withdrawn from treatment because of intolerable side effects. Patients in the chronic atrial fibrillation category who could not be successfully converted to sinus rhythm with direct current shock were arbitrarily assigned a short follow-up time of 0.001 month for the

purpose of constructing the actuarial curves described. Actuarial curves were compared using the Mantel-Haenszel form of the log-rank test. In addition, the relapse rate (17) (hazard function) measured in events per patient-month was calculated for various monthly intervals for each stage of treatment using the following formula:

$$\text{Relapse rate} = \frac{\text{Number of patients experiencing a relapse of atrial fibrillation}}{\text{Total observed follow-up time in patient-months during the interval}}.$$

For each stage of protocol, the average follow-up time in months was calculated as

$$\text{Average follow-up time} = \frac{\text{Sum of follow-up times for all patients entering stage}}{\text{Number of patients entering stage}}.$$

To estimate the success in maintaining sinus rhythm with our treatment program (consecutive treatments with propafenone followed by sotalol [conditional on prior failure with propafenone]), a separate actuarial curve was constructed. (This reflects our experience without resorting to alternative therapy.) The cumulative number of months free of treatment failure for this program was determined for each patient by assuming there was no delay in time from the point of failure during treatment with propafenone (stage 1) to enrollment in the sotalol trial (stage 2), treating the duration of follow-up for each patient free of failure in stage 1 or stage 2 as a censored event and utilizing the cumulative duration of follow-up on stage 1 plus stage 2 for all patients with an unsuccessful stage 1 who entered stage 2.

The proportion of patients classified as having chronic atrial fibrillation who underwent pharmacologic conversion to sinus rhythm during the various stages was compared using a two tailed Fisher's exact test. Assessment of correlates of response to treatment was restricted to atrial fibrillation pattern and left atrial size because these two baseline variables have consistently been identified as important prognostic markers of patient response. Statistical significance was taken at $p < 0.05$ for all analyses. Data are reported as mean values ± standard deviation unless otherwise indicated.

Results

Clinical characteristics of study group (Table 2). One hundred nine patients (70 men and 39 women) were enrolled in the trial. The scope of cardiac diagnoses was broad, but in 11% of the group no structural organic heart disease was detected (idiopathic atrial fibrillation). Fifty-three patients (49%) were classified as having chronic atrial fibrillation and 56 (51%) as having paroxysmal atrial fibrillation. A median of 24 months (range 0.3 to 576) had elapsed since atrial fibrillation was first documented on an ECG. The group had been unsuccessfully treated by a median of 2 previous drug programs (range 1 to 5). In the group of patients who had had an unsuccessful previous trial with quinidine (90% of patients), that previous trial was considered unsuccessful because of recurrence of atrial fibrillation in 53% of cases, intolerable side effects in 45% of cases and both recurrence of atrial fibrillation and intolerable side effects in 2% of cases. In the patients who had failed a previous trial of procainamide (63% of patients), that previous trial was considered unsuccessful because of recurrence of atrial fibrillation in 54% and intolerable side effects in 46%.

Table 2. Clinical Characteristics of the Study Group

	No.	%
Patients	109	M 64; F 36
Age (yr)	63 ± 13*	
Months since AF Dx	Median 24 (range 0.3 to 576)	
Cardiac Dx		
Hypertension	39	34
Valvular	32	29
CHF	29	27
Other	29	27
Idiopathic	12	11
Previous drug trials	Median 2 (range 1 to 5)	
Quinidine		90
Procainamide		63
Disopyramide		28
LA size (cm)	4.4 ± 0.9*	
LV EF	57 ± 14*	
Pattern†		
CAF	53	49
PAF	56	51

*Mean values ± SD; †In month before trial entry. AF = atrial fibrillation; CAF = chronic atrial fibrillation; CHF = congestive heart failure; Dx = diagnosis; EF = ejection fraction; F = female; LA = left atrial; LV = left ventricular; M = male; Other = sick sinus syndrome (SSS), pericardial or pulmonary disease, post coronary bypass graft surgery (CABG); PAF = paroxysmal atrial fibrillation.

The median left atrial anteroposterior dimension for the group was 4.5 cm (range 3.0 to 7.5, mean 4.4). Fifty-two individuals (48%) who had a left atrial dimension ≥4.5 cm were designated the *large left atrial group*; the 57 individuals (52%) with a left atrial dimension <4.5 cm were designated the *small left atrial group*. In the subset of patients with a paroxysmal atrial fibrillation pattern, the mean number of arrhythmic events per month at 12, 6 and 1 month before trial entry was 5.9 ± 13.5, 7.5 ± 13.9 and 14.5 ± 15.2, respectively. Of the 56 patients with paroxysmal atrial fibrillation, 28 (50%) had ≥10 episodes of atrial fibrillation in the month before trial entry, and these individuals were designated the *frequent paroxysmal atrial fibrillation group*. The other 28 patients in the paroxysmal atrial fibrillation group had <10 episodes of atrial fibrillation in the month before trial entry and were designated the *infrequent paroxysmal atrial fibrillation group*.

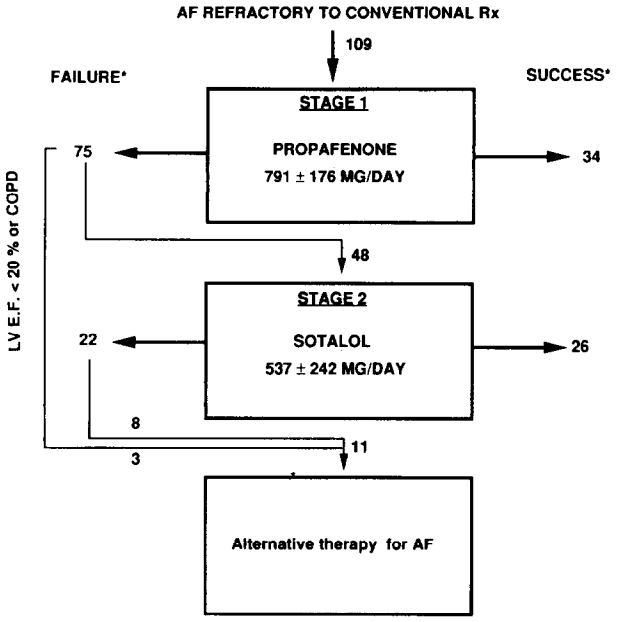


Figure 1. Flowchart of 109 patients with atrial fibrillation or flutter (AF) in two sequential drug trials, each stage being represented by a **box**. For each stage, the number of successes and failures is shown to the **right** and **left** of the boxes, respectively. The mean dosage of the drugs employed is recorded in each box. Patients with a left ventricular ejection fraction (LV E.F.) <20% or clinically significant chronic obstructive pulmonary disease (COPD), or both, were not eligible for treatment with sotalol and, therefore, were treated with alternative therapy (Rx) on failure of propafenone. *Failure = at least one recurrence of electrocardiograhically (ECG) documented atrial fibrillation (AF) or intolerable side effects; Success = no recurrence of ECG-documented symptomatic atrial fibrillation and no intolerable side effects.

Response to sequential stages of antiarrhythmic therapy. All patients were followed up for the duration of treatment while still receiving one of the therapeutic regimens; none was lost to follow-up. Each stage of the two sequential drug trials is summarized in Figure 1. Three individuals who were ineligible for sotalol treatment bypassed stage 2 and proceeded to alternative therapy after failure of stage 1. Not all patients with an unsuccessful propafenone trial advanced to the sotalol trial because of one or more of the following circumstances: patient refusal, nondrug-related death or failure to enter the next stage by the time of the data analysis. Eighty-five (78%) of the 109 patients followed the prescribed course of progressive advancement to sotalol after recurrence of atrial fibrillation or the development of intolerable propafenone-related side effects. Of the 24 patients (22%) who did not follow the prescribed course of therapy, 13 refused to adhere to the sequence of drug trials, 4 died of nondrug-related causes and 7 had not started on therapy in the next stage at the time of data analysis. There were no significant differences between the group of 24 patients who did not follow the full prescribed course and the group of 85 patients who did follow the course of treatment with regard to gender, age, number of months since original diagnosis of atrial fibrillation, pattern of atrial fibrillation in pretrial month, number of previous unsuccessful drug trials, left atrial size and left ventricular ejection fraction.

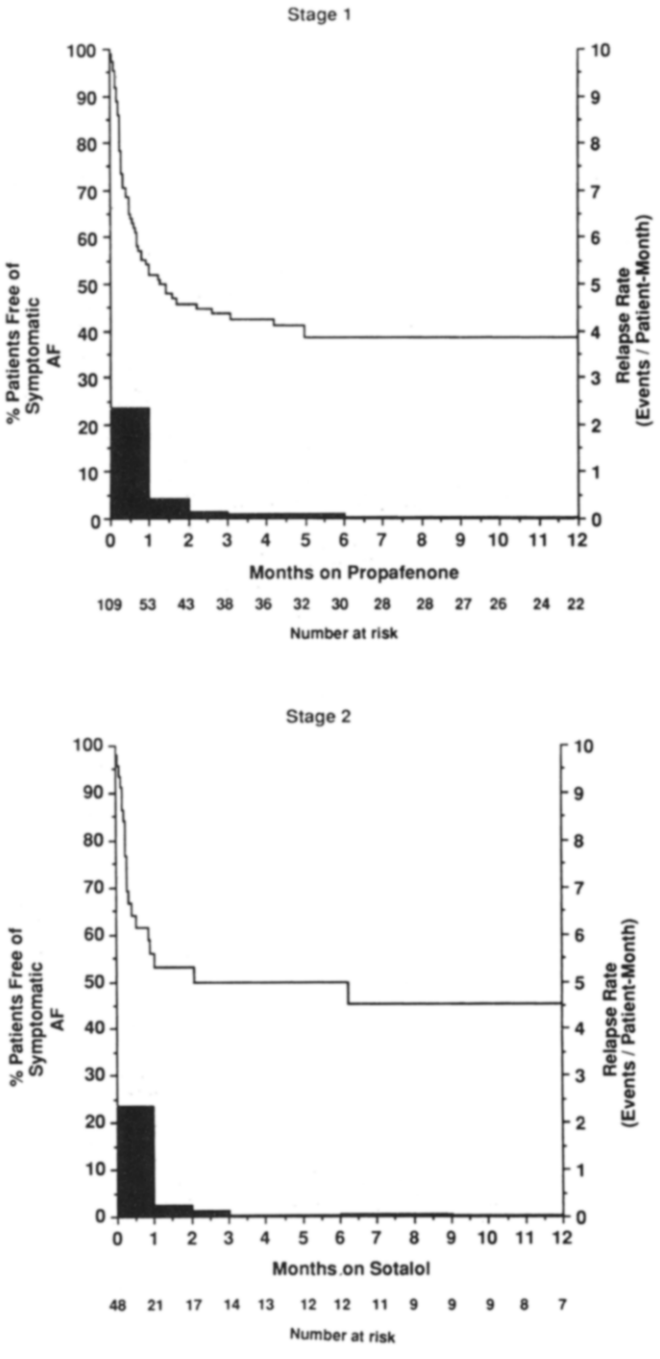
The average follow-up time and number of successfully treated patients for the sequence of drug trials were as follows: propafenone, 5.6 months (range 0.001 to 52.3), 34 of 109 patients; and sotalol, 3.9 months (range 0.001 to 27.3), 26 of 48 patients. Eight (8%) of the 97 instances of treatment failure during the two stages of the trial (sum of values on the left side of Fig. 1) were a result of intolerable side effects despite maintenance of sinus rhythm.

Among the patients with chronic atrial fibrillation treated with propafenone in stage 1, 3 (6%) of 53 had spontaneous reversion to sinus rhythm. Among the remaining patients treated with propafenone, atrial fibrillation was successfully terminated in all but one. A significantly greater proportion of the patients with chronic atrial fibrillation (7 [27%] of 26) had spontaneous pharmacologic conversion to sinus rhythm with sotalol during stage 2, as compared with propafenone during stage 1 ($p = 0.012$). All but one patient with chronic atrial fibrillation, who underwent direct current cardioversion in stage 2, also had restoration of sinus rhythm. The mean maintenance doses of antiarrhythmic medication during each of the stages of the protocol were 791 ± 176 mg/day for propafenone and 537 ± 223 mg/day for sotalol (Fig. 1).

Actuarial estimates of freedom from first symptomatic relapse of atrial fibrillation during each of the drug trials are compared in Figure 2. The curves show 1 year of follow-up data for all cases. By 6 months, approximately 39% of patients were free of recurrent atrial fibrillation while receiving propafenone (stage 1) as were 50% while receiving sotalol (stage 2). At each stage, clinical responses tended to remain relatively constant beyond 6 months. Because of the reduced number of patients followed up during propafenone and sotalol therapy after 12 months, estimates of the efficacy of these drugs after ≥1 year of therapy have wide confidence intervals. In each of the two trials, the atrial fibrillation recurrence rate was consistently highest during the first month of maintenance therapy; the first month recurrence rates were not significantly different between the two treatment strategies. Only infrequent late recurrences were noted during the remaining 9 months of the first year of follow-up (Fig. 2).

Cumulative success of treatment before initiation of alternative therapy and correlates of response to therapy. The cumulative proportion of patients successfully treated in the two drug trials is depicted in Figure 3. By 3 months, 59% of the total study group was still free of arrhythmia recurrence without resorting to alternative therapy. This proportion decreased slightly to 55% by 6 months and remained relatively constant beyond that point. The recurrence-free time curves (combining the first two stages) did not differ accord-

Figure 2. The **two panels** of this figure show the percent of patients free of symptomatic atrial fibrillation (AF) for each stage (stage 1 and stage 2) by time calculated according to Kaplan-Meier method (**left vertical scale**). The **bar graph** in the **lower portion of each panel** represents the estimated relapse rate or hazard function (**right vertical scale**) in relapses/patient-month, where each event represents an individual patient experiencing a recurrence to atrial fibrillation over the interval of time analyzed. The intervals analyzed included every month for the first 3 months and then 3 month blocks for the remaining 9 months of the first year. A rate of one relapse/patient-month corresponds to 23 relapses/100 patients per week. The number of patients at each time interval is listed at the **bottom**.



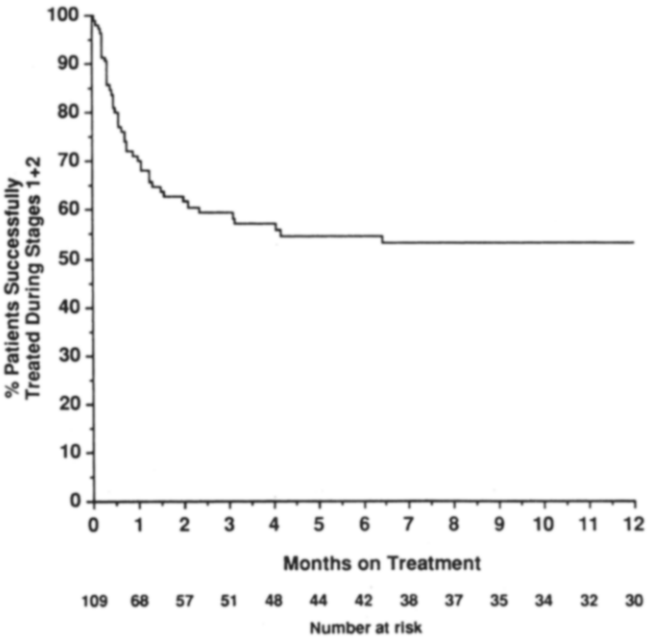


Figure 3. Actuarial curve depicting the proportion of patients who at analysis were free of symptomatic atrial fibrillation and in stage 1 or stage 2. For example, at 6 months, 55% of patients were free of symptomatic atrial fibrillation and in either stage 1 or stage 2. The number of patients at each time interval is listed at the **bottom**.

ing to patient subgroups classified by size of left atrium (small [median time to relapse of atrial fibrillation 4.1 months] versus large [median time to relapse of atrial fibrillation 4.2 months]), pattern of atrial fibrillation in the month before trial entry (chronic versus paroxysmal atrial fibrillation) and the number of episodes of atrial fibrillation in the month before trial entry (<10 versus ≥ 10 episodes). Furthermore, there were no detectable interactions among these factors.

Tolerability of long-term antiarrhythmic therapy (Table 3). Drug-related adverse reactions were seen in approximately 29% of patients. The majority of events were noncardiovascular, with neurologic disturbances (ataxia, dizziness, headache, blurred vision, fatigue) being the most common. Treatment with propafenone was associated with gastrointestinal complaints (constipation, epigastric discomfort) and a metallic taste in 13% and 7% of patients, respectively. Although a reduction in the heart rate at rest was common with sotalol, only 10% of patients developed symptomatic bradycardia, which in one case required insertion of a permanent dual chamber pacemaker to permit continued administration of the drug. Exacerbation of congestive heart failure was uncommon in both drug trials. No clinically significant deterioration in renal function developed during the course of the study protocol. One patient developed abnormal liver function tests after <2 months of therapy with propafenone;

Table 3. Drug-Related Side Effects

Side Effect	Propafenone Stage 1 (n = 109)	Sotalol Stage 2 (n = 48)
Cardiovascular (%)		
Bradycardia	3	10
CHF	3	2
Edema	0	2
Raynaud's	0	2
VT/VF	1	2
Exacerbation of AF	0	0
Noncardiovascular (%)		
CNS	10	19
GI	13	0
Impotence	0	2
Taste	7	0
Drug-related death (%)	0	0
With ≥1 side effect (%)	28	29
Drug stopped because of side effects (%)	7	8

CNS = central nervous system; GI = gastrointestinal; VT/VF = ventricular tachycardia/fibrillation; other abbreviations as in Table 2.

these normalized after cessation of the drug. One patient developed new onset of nonsustained ventricular tachycardia while receiving 900 mg/day of propafenone, which was no longer observed when the dose was reduced to 600 mg/day. One patient developed nonsustained torsade de pointes ventricular tachycardia during treatment with 560 mg/day of sotalol, necessitating discontinuation of that drug because lower doses of sotalol had not prevented recurrences of atrial fibrillation. No patient died of drug-related causes. Despite the development of drug-related side effects in approximately 1 in 4 patients during the course of the study, only 7% to 8% of patients (approximately 1 in 10) required termination of a stage of antiarrhythmic therapy because of intolerable adverse reactions.

Discussion

Although sinus rhythm can be restored at least transiently in the overwhelming majority of patients with atrial fibrillation by direct current cardioversion, the recurrence rate is high when no suppressive antiarrhythmic therapy is administered. It is estimated that only 15% to 40% of patients remain in sinus rhythm by 6 months after cardioversion; substantially fewer will be in sinus rhythm by the end of 1 year (18–28). Quinidine is still commonly regarded as the drug of choice for initial attempts at suppression of recurrent atrial fibrillation. However, data available from previous studies (19) suggest that only about 50% to 60% of quinidine-treated patients remain in sinus rhythm by 6 to 12 months. Of note, trials that provide estimates of quinidine's effectiveness often excluded patients with an enlarged left atrium, lengthy history of atrial fibrillation or a history of intolerance to quinidine preparations. Perhaps of even greater clinical relevance is the fact that quinidine preparations provoke adverse reactions in as many as 30% to 60% of patients and are often implicated in drug-induced episodes of ventricular proarrhythmia and sudden cardiac death, particularly in the presence of atrial fibrillation (29–31).

Major findings of the present trial. The present study suggests that propafenone and sotalol offer important therapeutic alternatives to quinidine. Despite a history of several unsuccessful drug trials with conventional type IA agents, including quinidine, a significant proportion of patients with recurrent symptomatic atrial fibrillation in this study could be treated successfully with new antiarrhythmic agents; approximately 55% were successfully treated for at least 6 months with sequential trials of propafenone and sotalol without having to resort to amiodarone therapy. Therapy with propafenone and sotalol was associated with a relatively low incidence of intolerable side effects which compares favorably with reported experience with quinidine preparations (29,30). Of interest was the observation that left atrial enlargement and a history of long-standing atrial fibrillation did not adversely affect the likelihood of successful treatment with propafenone and sotalol. This is in contrast to previous studies with quinidine in which these factors were predictive of poor outcome (21,23,26).

Approximately 25% of patients with chronic atrial fibrillation underwent spontaneous pharmacologic conversion to sinus rhythm during loading with sotalol. Although higher pharmacologic conversion rates have been reported (32–35) with high doses of quinidine (1 to 2 g orally over 5 to 10 h), this treatment was supplanted by direct current cardioversion because of an unacceptably high rate of side effects. The doses of quinidine currently employed in clinical practice have not been reported to achieve pharmacologic conversion rates as high as that seen for sotalol in this study (18).

For both drug trials, the relapse rate was highest during the first 3 months and then decreased sharply for the remainder of the first year of therapy. A similar pattern of an early high relapse rate has been reported with virtually every other trial of suppressive antiarrhythmic agent for atrial fibrillation regardless of agent employed (3,22,23,25). This pattern allows early identification of most patients who fail to be adequately treated with a given drug, enabling them to undergo trials with other agents without undue delay.

Our results should be viewed in the context of the nature of the patients' condition in the present trial. Although typical of the usual spectrum of clinical cardiology practice, the patients studied were selected by virtue of a history of failure of at least one trial with a type IA antiarrhythmic agent, a history of recurrent atrial fibrillation that was reliably associated with symptoms and, in most cases, well preserved left ventricular function. Individuals with an enlarged left atrium or a long history of symptomatic arrhythmia were not specifically excluded. Compared with enroll-

ment criteria of previously published studies of conventional drugs (21–26), the criteria in the present investigation were less restrictive and, therefore, should have biased our patient selection toward patients expected to be particularly refractory to suppressive antiarrhythmic therapy. Thus, the cumulative success in 55% of patients at the end of 6 months before trials of alternative therapy, coupled with the observation that nearly 90% of patients are free of intolerable drug-related adverse reactions, should be regarded as encouraging.

Although 24 patients (22% of the study group) did not follow the prescribed course of progression to successive stages conditional on failure of preceding stages, it is unlikely that the results would have been altered in any noteworthy manner if 100% of the study group followed the full protocol. The lack of any significant difference in baseline characteristics between those individuals who did and did not follow the full protocol suggests that the observed response rates were representative of the entire study group.

Possible mechanisms of antiarrhythmic drug effect. The precise electrophysiologic mechanisms by which antiarrhythmic agents exert their beneficial effects in suppressing atrial fibrillation in humans remain speculative. On the basis of the leading circle theory of atrial reentry and atrial fibrillation (11,36), antiarrhythmic drugs that result in a lengthening of the wavelength of a reentrant circuit should have antifibrillatory potential. Because wavelength is the product of conduction velocity times refractory period and because type III antiarrhythmic drugs such as sotalol have limited effect on conduction velocity in atrial tissue, it is likely that whatever beneficial effect these drugs have in suppressing atrial fibrillation stems from their ability to prolong the atrial effective refractory period (8). The beneficial effect of a type IC drug (such as propafenone) in suppressing atrial fibrillation is more difficult to explain because the principal effect of this drug is to slow conduction velocity, an effect that should cause a decrease rather than an increase in wavelength. It may be that because of the high drive rates of atrial fibrillation, propafenone causes a marked frequency-dependent decrease in atrial conduction velocity and that subsequent decremental conduction and extinction of circulating wave fronts is the mechanism by which this drug suppresses atrial fibrillation (37). As predicted by the work of Allessie and coworkers (11,36), prolongation of the atrial effective refractory period should be of greater importance than alteration of conduction velocity in preventing atrial fibrillation. Data from the present study support this hypothesis because many patients who failed to be adequately controlled with propafenone were controlled by sotalol. Furthermore, the rate of pharmacologic conversion to sinus rhythm was higher with sotalol than with propafenone. However, the nonrandomized nature of the sequence of therapies precludes definitive assessment of this hypothesis.

Methodologic considerations. Any study designed to evaluate the efficacy of treatment for atrial fibrillation must address a number of methodologic problems. Critically important among these is the problem of documenting cardiac rhythm before and after treatment. In the present trial, efficacy of drug therapy was assessed chiefly by a reduction in symptomatic recurrence of atrial fibrillation. Because both agents employed in this trial were capable of slowing the ventricular rate during atrial fibrillation, they may have caused some patients to be asymptomatic during recurrence of atrial fibrillation although they had been symptomatic before or during treatment with a drug used in an earlier stage. In contrast, documentation of all recurrences of atrial fibrillation, both symptomatic and asymptomatic, would have required continuous ECG monitoring for the entire follow-up period. Because of the expense and inconvenience involved, such an approach is impractical and unlikely to be implemented in a clinical trial. To enhance the detection of recurrent symptomatic episodes of atrial fibrillation in the present trial, we utilized telephone ECG transmitters, which obviated the need to obtain a 12 lead ECG or long-term ambulatory ECG in many patients (38). The telephone ECG system also afforded the opportunity to detect some asymptomatic recurrences during routine telephone transmissions. Of the 89 instances of a relapse of atrial fibrillation during the two stages of the trial, only 7 (8%) were asymptomatic; 3 of these were detected by telephone ECG and 4 were detected at routine office visits. Of these seven asymptomatic recurrences, only one occurred beyond 6 months. If we had not utilized the telephone ECG system, some of the asymptomatic recurrences would not have been diagnosed as promptly or at all. This would mean that our success rates would have been higher and the times to diagnosis of relapse of atrial fibrillation longer. Nevertheless, based on these detection rates of asymptomatic recurrences, our calculations of relapse rates may have underestimated the number of recurrences by about 10%. This would have reduced the proportion of successfully treated patients from the observed 55% to approximately 50% at 6 months.

Another methodologic problem any study of drug efficacy for suppression of atrial fibrillation must address is whether to use as an end point the number of relapses of atrial fibrillation during a period of observation or the time to first relapse of atrial fibrillation (39,40). Utilization of each patient as his or her own control requires comparison of pretrial relapse rate measurements with those obtained during therapy. This would have been suitable for patients with paroxysmal atrial fibrillation who do not require multiple cardioversions to restore sinus rhythm, but not for those with chronic atrial fibrillation. Because data on the details of previous unsuccessful therapy with type IA antiarrhythmic drugs were limited (especially in the chronic atrial fibrillation group), the fact that both patients with chronic or paroxysmal atrial fibrillation were enrolled and because of our desire

to apply the same measurement technique to both those with chronic or paroxysmal atrial fibrillation, we chose to monitor the time to first relapse (that is, arrhythmia-free interval). This approach had the additional advantages of not delaying treatment in symptomatic patients while pretrial observations were made and permitting assessment of multiple drugs in a short time interval when failures occurred. It should be pointed out, however, that such an approach did not permit strict comparison between the elaborate dosing and titration scheme utilized with the study drugs and the pretreatment therapy that had been deemed ineffective.

Clinical implications. Studies without internal controls such as the present one cannot form the basis of definitive therapeutic recommendations. However, they can provide useful information on current developments in medicine, pointing out important questions that can best be answered by randomized clinical trials. As outlined by Bailar et al. (41), observations made in studies relying on external controls, such as a previously described standard treatment, are considerably strengthened if such studies have five specific design features. All of these features can be found in the present study. The first feature is the likelihood that the intervention being applied will affect the outcomes reported or, in the present study, that better therapy for atrial fibrillation will be identified. Second, analysis of the results must be planned before generation of data. Our predetermined end point was measurement of the arrhythmia-free interval as analyzed by the life table method. Third, a plausible rationale must exist for interpretation of the data, such as the hypothesis that the electrophysiologic and pharmacologic profile of type IC and type III antiarrhythmic agents differs significantly from type IA agents. Fourth, the findings would be of interest even if "opposite" results had been obtained (for example, new drugs are less rather than more effective compared with standard treatment). Finally, there should be reasonable grounds for generalization of the results. In the present study, although the group of patients enrolled met a number of selection criteria, they were generally representative of patients commonly encountered in clinical cardiology practice. Based on the strength of the observations made in the present trial, it is clear that randomized clinical trials are now needed to determine whether new drugs such as those studied in this trial should be reserved for patients with refractory atrial fibrillation or should be offered as initial therapy.

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